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     (FILE 'HOME' ENTERED AT 11:40:25 ON 28 MAR 2002)

     FILE 'MEDLINE, BIOSIS' ENTERED AT 11:40:47 ON 28 MAR 2002
L1           166 S PDGF (S) IFN-GAMMA
L2            49 S L1 AND (HEAL? OR REPAIR OR COLLAGEN? OR FIBROSIS)
L3            29 DUP REM L2 (20 DUPLICATES REMOVED)
L4            22 S L3 AND PY<1999
L5            44 S ((PLATELET-DERIVED GROWTH FACTOR OR PDGF) AND
(INTERFERON-GAM
L6            28 DUP REM L5 (16 DUPLICATES REMOVED)
L7             0 S ((PLATELET-DERIVED GROWTH FACTOR OR PDGF) AND
(INTERFERON-GAM
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L4 ANSWER 1 OF 22 MEDLINE

TI Immunolocalization of cytokines and growth factors in oral submucous **fibrosis**.

AU Haque M F; Harris M; Meghji S; Barrett A W

SO CYTOKINE, **(1998 Sep)** 10 (9) 713-9.
Journal code: A52; 9005353. ISSN: 1043-4666.

AB Oral submucous **fibrosis** (OSF) is a chronic fibrotic disease of the oral cavity and oropharynx characterized by fibroelastic change in the mucosa which leads to progressive inability to open the mouth. The inflammatory cells in the lesional tissue consist mainly of T lymphocytes, with a high CD4:CD8 ratio, and major histocompatibility complex (MHC) class II expressing antigen-presenting cells. Cytokines and growth factors produced by inflammatory cells within the lesion may promote **fibrosis** by inducing proliferation of fibroblasts, upregulating **collagen** synthesis and downregulating **collagenase** production. The authors used a three-stage immunoperoxidase technique to investigate the expression of interleukin alpha (IL-1alpha) and beta, IL-6 interferon (IFN)-alpha, beta and gamma, transforming growth factor beta (TGF-beta), platelet-derived growth factor (**PDGF**) and basic fibroblast growth factor (bFGF) in frozen sections of OSF and compared it with that in normal buccal mucosa. The expression of cytokines and growth factors in normal tissues was consistent with their well known distribution and cell of origin, but the intensity and distribution in OSF were all, with the exception of IFN-alpha and gamma, upregulated with strong expression in both the epithelium and underlying connective tissue. IFN-alpha showed a similar pattern of staining in both normal mucosa and OSF. **IFN-gamma** showed little or no expression in most lesional tissues, suggesting an innate deficiency or downregulation of this cytokine. The general increase in pro-inflammatory cytokines and growth factors, and reduced production of **IFN-gamma**, may play an important role in the pathogenesis of OSF.

L4 ANSWER 5 OF 22 MEDLINE

TI Platelet-derived growth factor and inflammatory cytokines have differential effects on the expression of integrins alpha 1 beta 1 and alpha 5 beta 1 by human dermal fibroblasts in vitro.

AU Gailit J; Xu J; Bueller H; Clark R A

SO JOURNAL OF CELLULAR PHYSIOLOGY, **(1996 Nov)** 169 (2) 281-9.
Journal code: HNB; 0050222. ISSN: 0021-9541.

AB Dermal fibroblasts are essential for the **repair** of cutaneous wounds. Fibroblasts presumably use cell surface receptors of the integrin family during migration into a wound from the adjacent uninjured tissue and for the subsequent matrix **repairs**. We have investigated the possible roles of platelet-derived growth factor and inflammatory cytokines in the regulation of integrin expression on wound fibroblasts using a porcine cutaneous wound model and cultured human cells. Tissue specimens collected from 4-day pig wounds were stained with antibodies specific for the alpha 1 and alpha 5 integrin subunits. Staining for alpha 1 was markedly decreased on fibroblasts adjacent to the wound and in the granulation tissue, while staining for alpha 5 was clearly enhanced in both locations. Normal adult human dermal fibroblasts in culture express the integrins alpha 1 beta 1, a **collagen** receptor, and alpha 5 beta 1 a fibronectin receptor. Quantitative flow cytometry was used to measure cell surface integrin expression after treatment with platelet-derived growth factor (**PDGF**)-AA, **PDGF**-AB, or **PDGF** BB. Each isoform of **PDGF** produced a significant decrease in the level of alpha 1 present on the cell surface and an increase in the level of alpha 5. Furthermore, **PDGF**-BB produced a corresponding decrease in alpha 1 mRNA and an increase in alpha 5 mRNA. In contrast, treatment with three inflammatory cytokines, IL-1 beta, TNF-alpha, and **IFN-gamma**, produced clear increases in the levels of alpha 1 and alpha 5 present on the cell surface. Our observations suggest that the differential effects of **PDGF** and inflammatory cytokines may be part of the mechanism regulating the expression of alpha 1 and alpha 5 integrins by dermal fibroblasts during wound **repair**.

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L4 ANSWER 7 OF 22 MEDLINE

TI Cytokine expression in human cutaneous chronic graft-versus-host disease.

AU Ochs L A; Blazar B R; Roy J; Rest E B; Weisdorf D J

SO BONE MARROW TRANSPLANTATION, **(1996 Jun)** 17 (6) 1085-92.
Journal code: BON; 8702459. ISSN: 0268-3369.

AB Although chronic graft-versus-host disease (GVHD) remains a frequent complication of bone marrow transplantation (BMT), the pathogenesis remains unclear. We examined the potential role of cytokines in mediating chronic GVHD. Skin samples from seven patients with cutaneous chronic GVHD, six post-BMT controls and six normal controls were evaluated by reverse transcription polymerase chain reaction for the proinflammatory cytokines interleukin-1 alpha (IL-1 alpha) and tumor necrosis factor-alpha (TNF-alpha), Th1-associated cytokines IL-2 and interferon-gamma (**IFN-gamma**), Th2-associated cytokines IL-4, IL-5 and IL-10, and **fibrosis**-associated cytokines platelet derived growth factor (**PDGF**) and transforming growth factor-beta (TGF-beta). **IFN-gamma** transcription was significantly more frequent in cutaneous chronic GVHD (86%) vs post-BMT and normal controls (17% (P = 0.03) and 0 (P = 0.005), respectively). IL-2 transcription was more frequent in chronic GVHD (28%) and post-BMT controls (50%) vs normal controls (17%). TNF-alpha mRNA was frequent in chronic GVHD (71%) and post-BMT controls (83%), but not significantly more than in normal controls (50%). Transcription of IL-1alpha, IL-4, IL-5 and IL-10 was infrequent in all three groups. **PDGF** and TGF-beta mRNA were detected in the majority of all samples. The frequent transcription of **IFN-gamma** in cutaneous chronic GVHD supports its potential role in mediating the associated tissue injury. While the cellular sources of these cytokines are uncertain, their expression and secretion in situ may propagate the cytotoxic cascade and perpetuate the tissue injury. Better understanding of the contribution of FN-gamma and other cytokines to the pathogenesis of chronic GVHD may allow the design of more specific and more effective therapy.

L6 ANSWER 10 OF 28 MEDLINE DUPLICATE 6
TI **Interferon-gamma** modulates lung macrophage production of **PDGF**-BB and fibroblast growth.
AU Badgett A; Bonner J C; Brody A R
SO JOURNAL OF LIPID MEDIATORS AND CELL SIGNALLING, (1996 Jan) 13 (1) 89-97.

Journal code: B1W; 9430888. ISSN: 0929-7855.
AB Platelet-derived growth factor (PDGF) is a potent mediator of fibroblast proliferation and chemotaxis. We have studied here the cytokine interferon-gamma (IFN-gamma) which is known to prime macrophages for increased PDGF production. Thus, we postulated that IFN-gamma would act as a positive regulator of PDGF-BB secretion by rat alveolar macrophages, and in addition we asked whether or not the IFN-gamma (a known anti-mitogenic cytokine) would block the growth response of primary lung fibroblasts to the PDGF-BB. Macrophages incubated with IFN-gamma or iron spheres alone for 24 h secreted 2.5-fold more PDGF-BB than control macrophages incubated in serum-free medium. Preincubation of macrophages with IFN-gamma prior to the addition of iron spheres synergistically increased PDGF-BB production 2-10-fold after 24 h. In contrast, when IFN-gamma was added to quiescent rat lung fibroblasts (RLFs) in the presence of PDGF-BB, the cytokine induced a concentration-dependent decrease in cell growth, while IFN-gamma alone did not affect proliferation. [125I]PDGF-BB receptor assays showed that neither preincubation nor coincubation of RLF with IFN-gamma affected PDGF-BB binding to its receptors.

L6 ANSWER 12 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI **Platelet-derived growth factor** and inflammatory cytokines interleukin-1-beta, tumor necrosis factor-alpha, and **interferon-gamma** have differential effects on integrin receptors for collagen and fibronectin.
AU Gailit, J.; Clark, R. A. F.
SO Journal of Investigative Dermatology, (1994) Vol. 102, No. 4, pp. 631.
Meeting Info.: Annual Meeting of the Society for Investigative Dermatology
Baltimore, Maryland, USA April 27-30, 1994
ISSN: 0022-202X.

L6 ANSWER 16 OF 28 MEDLINE DUPLICATE 10
TI Up-regulation of alveolar macrophage **platelet-derived growth factor**-B (**PDGF**-B) mRNA by **interferon-gamma** from Mycobacterium tuberculosis antigen (PPD)-stimulated lymphocytes.
AU Wangoo A; Taylor I K; Haynes A R; Shaw R J
SO CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1993 Oct) 94 (1) 43-50.
Journal code: DD7; 0057202. ISSN: 0009-9104.
AB Macrophage production of PDGF-B is believed to be important in the pathogenesis of diseases where chronic lung inflammation develops into fibrosis. Since tuberculosis is characterized by chronic inflammation and tissue fibrosis, we asked if lymphokines from lymphocytes stimulated by the Mycobacterium tuberculosis antigen PPD, contained factors capable of increasing human alveolar macrophage PDGF-B mRNA. Supernatants from both phytohaemagglutinin (PHA)- and purified protein derivative (PPD)-stimulated lymphocytes, when added to macrophages, induced an increase in the mRNA of PDGF-B, but not transforming growth factor-beta (TGF-beta). When lymphocytes from contacts of patients with tuberculosis, patients with tuberculosis, and normal subjects were compared following PPD stimulation, the lymphocytes from the contacts had the greatest proliferation response, the greatest production of interferon-gamma (IFN-gamma), and their lymphokines induced the greatest increase in PDGF-B mRNA in macrophages. Recombinant human IFN-gamma reproduced this ability of lymphokines to increase macrophage PDGF-B mRNA. Finally, the increase in macrophage PDGF-B mRNA following incubation with supernatants from PPD-stimulated lymphocytes was shown to be due to IFN-gamma, when the increase in macrophage PDGF-B mRNA was prevented by addition of anti-human IFN-gamma antibody to the lymphocyte supernatant. This study indicated that antigen-stimulated lymphocytes released IFN-gamma, which in turn resulted in an increase in PDGF-B mRNA in alveolar macrophages. Such a mechanism provides a link between the DTH response and the first stages of a fibrotic reaction, and may offer an explanation for the progression of chronic inflammation to fibrosis, as occurs in the lungs of patients with untreated pulmonary tuberculosis.

L6 ANSWER 18 OF 28 MEDLINE DUPLICATE 11
TI **Interferon-gamma** suppresses **PDGF** production from THP-1 cells and blood monocyte-derived macrophages.
AU Kosaka C; Masuda J; Shimokado K; Zen K; Yokota T; Sasaguri T; Ogata J
SO ATHEROSCLEROSIS, (1992 Nov) 97 (1) 75-87.
Journal code: 95X; 0242543. ISSN: 0021-9150.
AB Involvement of the immunological mechanisms in atherogenesis has recently been suggested by immunohistological detection of macrophages and T lymphocytes in atherosclerotic lesions. In the present study, we have investigated the regulatory effect of interferon-gamma (IFN-gamma), a cytokine secreted by activated T cells, on the production and secretion of platelet-derived growth factor (PDGF) from macrophages in culture. The human monocytic leukemia cell line, THP-1, was treated with phorbol 12-myristate 13-acetate (PMA) for 24 h to induce macrophage differentiation and PDGF production, and then various doses of recombinant human IFN-gamma (0-1000 I.U./ml) were added to the culture. After 48 h, the conditioned medium and the cells were harvested and analyzed for PDGF production. PDGF-dependent mitogenic activity in the conditioned medium, estimated by neutralization of mitogenic activity with anti-PDGF antibody,

was suppressed by IFN-gamma treatment. Radioimmunoassays for PDGF also revealed a decrease in both PDGF-AA and -BB in the conditioned medium with IFN-gamma treatment, whereas neither total cell DNA as an indication of cell number nor overall protein synthesis based on [3H]leucine incorporation were decreased. Northern analysis of total RNA extracted from the cells demonstrated that IFN-gamma suppressed the level of PDGF mRNA. Analysis of mRNA degradation in the presence of actinomycin D demonstrated that the decrease in PDGF mRNA was not due to enhanced degradation of mRNA. A similar inhibitory effect of IFN-gamma on PDGF mRNA levels was also found in monocyte-derived macrophages cultured in the presence of granulocyte-macrophage colony stimulating factor. These results suggest that IFN-gamma modulates production and secretion of PDGF from macrophages and that the functions of macrophages in atherogenesis may be regulated by the cellular interactions between T cells and macrophages through the action of cytokines such as IFN-gamma.

L6 ANSWER 23 OF 28 MEDLINE
TI Pathogenesis of pulmonary fibrosis in interstitial lung disease. Alveolar macrophage **PDGF**(B) gene activation and up-regulation by **interferon gamma**.
AU Shaw R J; Benedict S H; Clark R A; King T E Jr
SO AMERICAN REVIEW OF RESPIRATORY DISEASE, (1991 Jan) 143 (1) 167-73. Journal code: 426; 0370523. ISSN: 0003-0805.
AB Alveolar macrophages are believed to be central in orchestrating the fibrotic response in interstitial lung disease (ILD). To test the hypothesis that macrophages from patients with ILD were dedicated to growth factor production and that this was independent of other indices of macrophage activation, we measured the mRNA of the B chain of PDGF and TGF-beta, as well as HLA-DR-alpha in alveolar macrophages from patients with ILD and from normal control subjects. When alveolar macrophages were examined immediately after lavage, cells from patients with ILD had increased PDGF(B) but similar TGF-beta and HLA-DR-alpha mRNA when compared with control subjects. Discoordinate regulation of these genes was observed when alveolar macrophage PDGF(B) mRNA increased while TGF-beta and HLA-DR-alpha mRNA decreased after culture for 24 h. This response was not disease-related as these changes were similar in cells from patients with ILD and from control subjects. Because a lymphocytic alveolitis is present in many cases of ILD, we asked whether interferon gamma (IFN-gamma) modulated the activation of these genes. In both the patients and the control subjects, PDGF(B) and HLA-DR-alpha, but not TGF-beta, mRNA were increased after incubation with IFN-gamma. These results indicate that PDGF(B) mRNA may be increased in alveolar macrophages in ILD and that PDGF(B), TGF-beta, and HLA-DR-alpha are independently regulated genes in alveolar macrophages, but that IFN-gamma increases both PDGF(B) and HLA-DR-alpha mRNA. We speculate that IFN-gamma induced PDGF(B) gene activation may be an important mechanism by which lymphocytes promote pulmonary fibrosis.

L6 ANSWER 25 OF 28 MEDLINE DUPLICATE 14
TI Inhibition of mitogenic activity of **PDGF**, EGF, and FGF by **interferon-gamma**.
AU Oleszak E
SO EXPERIMENTAL CELL RESEARCH, (1988 Dec) 179 (2) 575-80. Journal code: EPB; 0373226. ISSN: 0014-4827.
AB Natural or recombinant human interferon-gamma abolishes the mitogenic activity of platelet-derived growth factor, epidermal growth factor, and fibroblast growth factor on GM2767 or FS-4 human fibroblasts. Similarly murine interferon-gamma abolishes the mitogenic activity of these growth factors on BALB/C-3T3 fibroblasts. Inhibition of DNA synthesis by interferon-gamma was accomplished by blocking the transition of G0/G1 to S phase of the cell cycle. Addition of interferon-gamma 15 h after the addition of growth factors (when the cells had already entered the S phase) had no effect on DNA synthesis.

L6 ANSWER 26 OF 28 MEDLINE DUPLICATE 15
TI Recombinant **interferon-gamma** inhibits the mitogenic effect of **platelet-derived growth factor** at a level distal to the growth factor receptor.
AU Hosang M
SO JOURNAL OF CELLULAR PHYSIOLOGY, (1988 Mar) 134 (3) 396-404.

Journal code: HNB; 0050222. ISSN: 0021-9541.
AB Highly purified preparations of recombinant human interferons (rIFNs)-alpha A, -beta, and -gamma all inhibited platelet-derived growth factor (PDGF)-induced DNA synthesis in normal human dermal fibroblasts, as monitored by incorporation of [3H]-thymidine into trichloroacetic acid (TCA)-insoluble material. rIFN-gamma was the most potent, since it blocked the PDGF response by 50% at about 10 U/ml or 0.3 ng/ml, whereas with rIFN-alpha A and rIFN-beta 4000 U/ml and 600 U/ml, respectively (10 ng/ml in both cases), were required to achieve the same effect. There was a close parallelism between the ability of these rIFNs to inhibit PDGF mitogenic activity and their capacity to inhibit cell proliferation in serum-containing medium. None of the rIFNs inhibited specific binding of 125I-PDGF to fibroblasts, and none interfered with receptor internalization. The mechanism of action of rIFN-gamma was analyzed further. rIFN-gamma did not inhibit uptake of [3H]-thymidine into these cells. However, it shifted if the time point of initiation of DNA synthesis from about 14 h after stimulation with PDGF to about 18 to 21 h and decreased significantly the rate of the DNA synthesis. rIFN-gamma could be added up to 6 h following stimulation with PDGF with no loss of its inhibitory effect. rIFN-gamma also blocked the mitogenic activity of epidermal growth factor and basic fibroblast growth factor. Taken together these results implicate that rIFN-gamma exerts its antimitogenic effect by inhibiting a process that occurs late in the PDGF signaling pathway and onto which the activity pathways of other mitogens converge. In view of the important role PDGF may play in wound-healing and in the pathogenesis of the proliferative lesions of arteriosclerosis, these data point to a possible role IFN-gamma may play as a regulator of these processes in vivo.

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